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Stable Ischemic Heart Disease in Women

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Abstract

Purpose of the review Paradoxically, although women have a lower burden of coronary atherosclerosis, they experience more symptoms, more frequent hospitalizations, and a worse prognosis compared to men. This is in part due to biological variations in pathophysiology between the two sexes, and in part related to inadequate understanding of these differences, subconscious referral bias, and suboptimal application of existing women-specific guidelines. We sought to review the contemporary literature and provide an update on risk assessment, diagnosis, and management of IHD in women.
Recent findings IHD in women is often secondary to diffuse non-obstructive atherosclerosis, coronary spasm, inflammation, and endothelial and microvascular dysfunction, and less commonly due to the male pattern of flow-limiting epicardial stenosis. Both IHD patterns likely represent sex-specific manifestations of the same disease process. Additionally, there is a differential expression of risk factors and symptoms between men and women. Application of male-pattern IHD risk factors and presentation to women contributes to under-recognition, under-testing, and under-treatment of IHD in women compared to men. Traditional diagnostic evaluation has focused on detection of epicardial disease, amenable to revascularization. Our improved understanding of sex-specific pathophysiology of IHD has enabled us to also develop tools for detection of microvascular disease. Advances in stress MRI, flow quantification on stress PET, and provocative invasive angiography have filled this void and offer important diagnostic and prognostic information.

Summary Despite our improved understanding of sex-specific differences in presentation, risk factors, pathophysiology, diagnostic testing, and management strategies of IHD, women with IHD continue to experience worse outcomes than men. This disparity underscores the need for improved research and understanding of biological sex differences, elimination of subconscious gender bias in referral patterns, and improved application of existing research into clinical practice.

Introduction

Ischemic heart disease (IHD) is the leading cause of death for women worldwide [1]. This statistic is no different in the United States (US), where IHD accounted for nearly 160,000 female deaths in 2015 [1]. Recent estimates demonstrate that 7.4 million women in the US are living with IHD [1]. Owing in part to national educational campaigns, there has been improved awareness, recognition, and treatment of IHD in women since 1979, resulting in an initial decline in female mortality. However, awareness of the burden of IHD in women, its risk factors, and recognition of symptoms remain subpar in both the lay and medical communities [2]. In 2012, only 56% of women were aware of IHD being their leading cause of death [1].

As a result, perhaps, since 2010, mortality trends in women seem to have stabilized, and more concerningly appear to be on the rise [1]. Certain subsets of women, particularly the young (< 55 years old) and ethnic minorities continue to experience worse outcomes compared to age-matched men [1, 3]. Women are still less likely to receive preventive and guideline-directed care than men with similar ASCVD risk scores [3]. When prescribed appropriate therapies, women are also less likely to be treated aggressively and are less likely to achieve optimal effects from these therapies, underscoring a disparity in diagnosis and management of IHD in women [3].

This review outlines the contemporary data on the sex-specific differences in pathophysiology, clinical presentation, traditional and novel risk factors, diagnostic evaluation, and management strategies for stable IHD in women. Contemporary challenges in diagnosis and management of IHD in women that contribute to ongoing disparities are highlighted.

Impact of ischemic heart disease

As the number one cause of death in both men and women in the US [4], IHD has a huge impact on healthcare costs. Cardiovascular disease accounted for 14% of the total health expenditure between 2013 and 2014, with hospitalization for IHD being a major contributor to this [1]. These costs are projected to increase > 100% by 2035 [1]. In 2013, hospitalizations for IHD, including myocardial infarction, were among the most expensive [1]. Women with IHD have higher resource utilization as evident by more office visits, more avoidable hospitalizations, and higher rates of recurrent angina, heart failure, and myocardial infarction (MI) mortality, compared to men [5]. Compared to men, women with angina have inferior functional status scores, even after adjusting for comorbidities and severity of IHD [6]. This in turn translates to higher healthcare costs and potentially poor compliance, highlighting the substantial impact that IHD has in women, not only at an individual level but also at the population level [7].

Risk factors and risk assessment

Traditional cardiovascular risk factors are overall similar between the sexes. The nine risk factors identified in the INTERHEART study: abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, consumption of fruits, vegetables, and alcohol, and regular physical activity account for 94% of the risk of MI in women and 90% in men [8]. Biological differences between men and women may affect the expression of cardiovascular risk factors, and impart a differential risk for women (Table 1). For instance, smoking, hypertension, diabetes, and physical inactivity have a higher odds ratio of predicting risk of MI in women compared to men [8, 9]. The cumulative effect of the conventional modifiable risk factors confers a nearly 2-fold relative increased risk of MI in older women and 8-fold increased risk in younger women compared to men, highlighting the importance of primary prevention in young women [8]. Table 1 highlights novel cardiac risk factors that are unique to women including early

Table 1. Association of risk factors with IHD in women

Risk factor	Risk of IHD in women
Smoking	• Smoking confers a 2-fold increased risk of MI in women compared to men [9]. • There is an increased risk of venous thrombosis and MI in women who smoke with concomitant oral contraceptive use [10]. • Although women have a lower prevalence of tobacco use than men, the decline in smoking has been less pronounced in women [10].
Hypertension	• Hypertension is more common in women than men, particularly in black women, obese, and those on oral contraceptives [10]. • Hypertension is associated with a 1.5-fold increased risk of MI in women compared to men [8]. • A 3-fold increase in IHD and stroke is seen in women with SBP > 185 mmHg, compared to normotensive women [10].
Hyperlipidemia	• Menopause is associated with a worsening lipid profile in women [11]. • Hypertriglyceridemia confers a 2-fold increased risk of IHD in women compared to men [12].
Diabetes	• Diabetes is associated with a 1.6 times increased risk of MI in women [8].
Obesity	• The rate of obesity is similar among women and men; however, extreme obesity (BMI > 40) is more than twice as common among women [13]. • The incidence of obesity may be as high as 40% in post-menopausal women who predominantly accumulate visceral fat, compared to younger women, which increases the risk of IHD [9, 14].
Psychosocial factors	• There is a 2-fold higher prevalence of depression in women [14]. • Presence of depression is associated with a 50% increased risk of adverse cardiac events and worse quality of life [10].
Autoimmune disorders	• IHD risk is almost 60% higher in patients with rheumatoid arthritis after correcting for other risk factors [15]. • IHD is the leading cause of mortality and morbidity in women with systemic lupus erythematosus, with a two times higher risk of MI compared to age-matched peers with SLE [9]. • Treatment of autoimmune disorders involves corticosteroids, which are associated with increased risk of premature atherosclerosis [9].
Pregnancy-related disorders	• Presence of gestational diabetes, pre-eclampsia, eclampsia, and pre-term delivery are all associated with increased IHD risk [9]. • History of preeclampsia confers a nearly 2-fold higher risk of IHD, stroke, and venous thromboembolic events [14]. • Gestational diabetes is associated with a 59% increased risk of MI [16].
Radiation therapy	• Chest wall radiation after breast cancer is associated with increased risk of IHD, particularly coronary calcification [17, 18]. • Rate of IHD events increase linearly with the mean radiation dose to the heart by 7.4% per gray of radiation [19].
Early menopause	• Early menopause confers a 4.5 times higher risk of IHD [20].

IHD ischemic heart disease, *MI* myocardial infarction, *SBP* systolic blood pressure, *BMI* body mass index, *SLE* systemic lupus erythematosus

menopause or menarche, gestational diabetes, pregnancy-related hypertension, autoimmune disorders, and psychosocial stresses [9, 16, 20–22, 23••]. The importance of incorporating these risk factors is increasingly being recognized, and both American and European cardiology societies have made recommendations for consideration of these novel risk factors in assessing a woman's risk [23••, 24] (Table 1).

Despite 48% of women having three or more traditional risk factors for IHD [10], discussion of risk factors and individual risk assessment does not occur consistently in women [25••]. Multiple calculation tools exist

to predict the risk of IHD; most do not account for the sex-based differential risk of the traditional risk factors [26, 27]. The American Heart Association and American College of Cardiology (AHA/ACC)'s atherosclerotic cardiovascular disease (ASCVD) risk assessment tool is perhaps the most widely used and distinguishes risk based on sex [28]. It, however, does not factor in any of the novel risk factors specific to women [28]. Despite the higher number of risk factors, most global risk scores underestimate the true risk and characterize a greater percentage of women as 'low risk" compared to their male peers [29]. There are also no clear recommendations on how to incorporate novel risk factors into risk scores, except for the European Society of Cardiology's recommendation to use a 1.5 multiplier in rheumatoid arthritis and autoimmune disease [23••].

Clinical presentation

Biological variations including differences in coronary artery size, hormonal influences, autonomic innervation, and hematologic and electrophysiologic indices contribute to differences in symptom presentation of IHD between men and women [30] (Fig. 1). Only 31% of young women present with chest pain, compared to 42% of men [31, 32]. The evaluation of symptomatic women is hampered by use of the definition of "typical angina" in traditional models such as the Diamond-Forrester tools [33]. These risk models are derived from large cohorts of men and are more reflective of the male pattern of exertional chest pain. Among patients diagnosed with acute coronary syndromes, women were less likely to report typical chest pain and were more likely to report atypical chest pain, abdominal discomfort, loss of appetite, dyspepsia, nausea, vomiting, dyspnea, hand numbness, palpitations, dizziness, fatigue, or weakness [31, 32, 34]. Presence of these nonspecific symptoms and vague presentations further hamper the timely recognition and diagnosis of IHD in women [31, 34]. In particular, younger women often present with absence of chest pain, have a delayed presentation, and suffer worse outcomes [32, 34, 35].

Pathophysiology

The dynamic interaction of hormonal influences, atypical risk factors, and smaller, more vasoreactive coronary arteries in women result in a female-specific phenotype

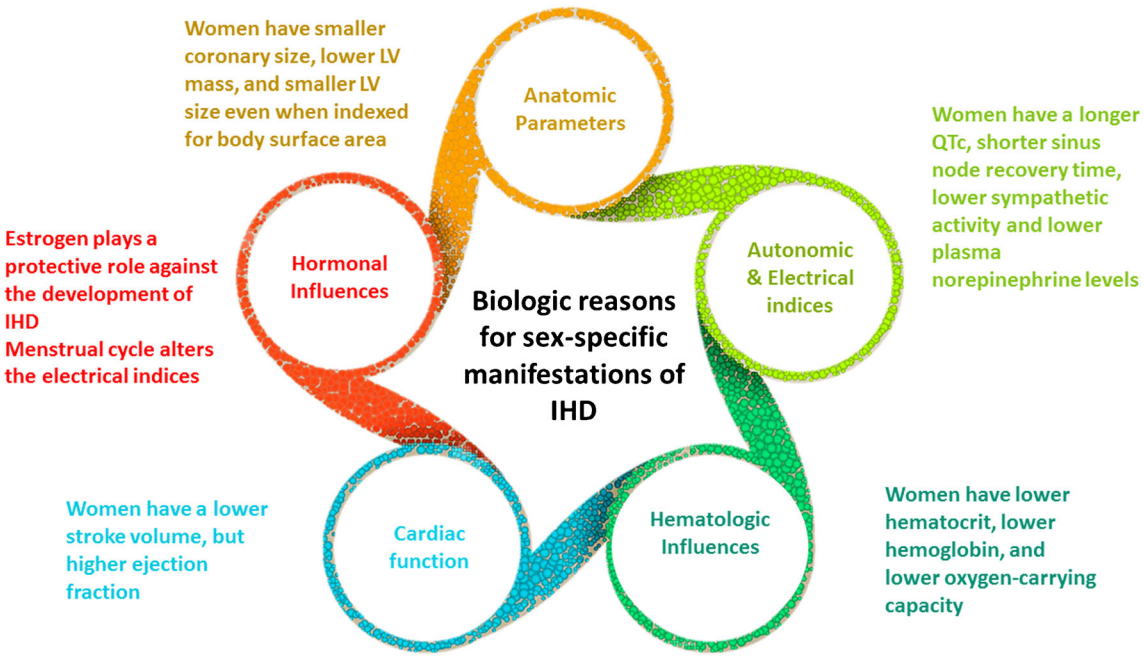

Fig. 1. Biologic reasons for sex-specific manifestations of ischemic heart disease. Biologic reasons for sex-specific manifestations of ischemic heart disease include difference in anatomic parameters, autonomic and electrical indices, hematologic factors, cardiac function, as well as hormonal influences. LV left ventricle, QTc corrected QT interval, IHD ischemic heart disease.

of IHD [36]. Symptomatic women are less likely to experience the traditionally described male pattern of flow-limiting epicardial atherosclerosis [37]. Instead, they are more prone to epicardial and microvascular spasm, vascular inflammation, myocardial bridging, and dysfunction of the endothelium and microvasculature [37–40]. Women have a lower atheroma burden and exhibit more diffuse, less obstructive disease compared to men [39, 41]. Thus, symptomatic women at risk for IHD frequently (60–70%, compared to ~ 30% men) have angiographically normal coronaries or non-obstructive disease on invasive coronary angiography (ICA) [37, 42].

The appearance of normal coronaries on ICA may be misleading, as women may still have a high burden of microvascular disease that portends an adverse prognosis [43•]. Normally, the coronary flow increases 2.5–5-fold in response to physiologic or pharmacologic stress (coronary flow reserve (CFR)) [44]. However, patients with microvascular dysfunction are unable to increase coronary flow due to impaired reactivity of the coronary microvasculature, resulting in reduced CFR and myocardial perfusion and ultimately myocardial ischemia [45]. Microvascular disease, while present in men, is far more prevalent in women [39]. Although the traditional IHD risk factors are implicated in development of microvascular disease, the exact mechanism for its development and progression is poorly understood.

While both macrovascular and microvascular coronary disease may operate independently, they more frequently operate in concert and have been hypothesized to be a continuum of sex-specific response to vascular injury [41]. Consequently, to accommodate the full spectrum of coronary atherosclerosis in women, the term IHD is more apt.

Sex hormones play a key role in the differential expression of IHD between the sexes. Premenopausal women have a lower incidence of IHD compared to age-matched men, but the incidence of IHD steeply rises following menopause [10]. Estrogen plays a protective role against the development of atherosclerosis by inhibiting smooth muscle proliferation, matrix deposition, and promoting re-endothelization following vascular injury [46]. However, exogenous hormone replacement therapy after menopause is not beneficial in delaying progression of atherosclerosis and has not resulted in improving cardiac mortality [47].

Diagnostic evaluation of stable IHD in women

The AHA's statement on the role of non-invasive testing for women with suspected IHD provides a sex-specific algorithm that incorporates both functional stress imaging and anatomic imaging [48••]. Functional stress testing includes exercise treadmill testing (ETT), echocardiography, single-photon emission computed tomography (SPECT), positron emission tomography (PET), myocardial perfusion imaging (MPI), and cardiac magnetic resonance imaging (CMR); in contrast, anatomic assessment relies on coronary computed tomography angiography (CCTA) and ICA. Contemporary guidelines on diagnosing IHD predominantly focus on stress imaging techniques that traditionally look for hemodynamically significant luminal stenosis, warranting revascularization [48••, 49]. Advances in our understanding of the pathophysiology of IHD in women have rendered these algorithms inadequate. Although a stress test may exclude epicardial stenosis in symptomatic women, they often continue to experience symptoms and high mortality, underscoring the need to supplement our testing with additional imaging to explore the full spectrum of IHD that encompasses evaluation of obstructive and non-obstructive plaque, and dysfunction of the coronary microvasculature and endothelium [50, 51].

The basis of choosing the appropriate diagnostic test to evaluate for IHD in women depends on a number of factors, including test availability, local expertise, patient age, body habitus, ability to exercise, and an individual's risk profile and pretest probability of having IHD [48••]. Women at low risk for IHD are generally not considered candidates for further diagnostic testing. Given that ETT is cheap, readily available, and has high negative predictive value, it is recommended as the first-line test in symptomatic women at an intermediate risk for IHD, with a normal resting ECG and able to perform maximal exercise [48••]. However, women have a higher proportion of obesity and physical inactivity, and are consequently unable to produce maximal exercise, and have ECG changes related to hormonal influences, all of which result in lower diagnostic accuracy with ETT compared to imaging studies [14, 48••, 52]. Symptomatic women at intermediate-to-high risk for IHD, with resting ST segment ECG abnormalities or unable to exercise, are generally referred for stress imaging to assess for stress-induced wall motion or myocardial perfusion abnormalities [48••]. Table 2 highlights the advantages and disadvantages of each modality, along with the sensitivity and specificity of detecting obstructive atherosclerosis in women [53].

Table 2. Advantages, disadvantages, and diagnostic accuracies of testing modalities for IHD in women

Modality	Advantages	Disadvantages	Sensitivity[a]	Specificity[a]
ETT	Cheap, readily available Large body of diagnostic and prognostic literature	Lower diagnostic accuracy Not feasible in patients with abnormal ECG or limited exercise capacity	62% [53]	68% [53]
Echocardiogram	No exposure to ionizing radiation Both exercise and pharmacologic stress are feasible High temporal resolution Portable, widely available	Limited by acoustic windows Operator dependent	79% [53]	83% [53]
SPECT	Widely available Lower spatial resolution Large body of diagnostic and prognostic literature	Radiation exposure Lengthy exams Breast attenuation artifact can be a real challenge	81% [53]	78% [53]
PET	Lower radiation exposure, higher spatial resolution, less readily available compared to SPECT Most apt for obese women, and suspected microvascular disease	Radiation exposure	81% [54]	86% [54]
MRI	High spatial resolution No exposure to ionizing radiation 3D data sets, not limited by anatomic boundaries High diagnostic accuracy	Not feasible with claustrophobia Imaging in pts. with devices and renal failure a challenge	72% [53]	84% [53]
CCTA	Direct visualization of the burden, location and composition of coronary plaque 3D data sets, not limited by anatomic boundaries	Radiation exposure Side effects of contrast (renal failure, allergy)	94% [53]	87% [53]
Coronary angiogram	Direct visualization of coronary lumen Can combine with FFR and IVUS to identify hemodynamically significant lesions	Invasive	NA	NA

[a]Compared to coronary angiography

ETT exercise tolerance testing, *SPECT* single photon emission computed tomography, *PET* positron emission tomography, *MRI* magnetic resonance imaging, *CCTA* coronary computed tomography angiography, *ECG* electrocardiogram, *FFR* fractional flow reserve, *IVUS* intravascular ultrasound

Stress echocardiography

Stress echocardiography confers a higher diagnostic accuracy than ETT [55] and is predictive of IHD events in women, including MI and death, even in the absence of obstructive coronary artery disease (CAD) on angiography [56, 57]. A 2-year cardiac event-free rate of 97% was observed in those with a stress echocardiogram, while an abnormal study was associated with a 4-fold higher risk of cardiac events [57, 58].

Stress myocardial perfusion imaging

Stress MPI, with either SPECT or PET, offers comparable diagnostic accuracy to stress echocardiography [58]. However, its use may be limited in younger women due to the exposure to ionizing radiation. Improvements in scanning protocols, scanner types, and isotopes have improved versatility with resultant radiation doses as low as 1 mSv [59]. In addition to high diagnostic accuracy, stress MPI offers incremental prognostic value over clinical variables, ECG and LVEF in symptomatic women at risk for IHD [60, 61]. A normal stress MPI scan is associated with < 1% annual cardiac event rate compared to over 3-fold with abnormal MPI study in women [61].

Compared to SPECT, PET imaging, owing to its higher spatial resolution and inbuilt attenuation correction, reduces breast attenuation artifacts commonly seen in obese women, and allows for improved visualization of small perfusion defects, particularly in women who generally have smaller hearts, with lower radiation exposure [54, 60, 62]. Stress MPI with PET also allows for the evaluation of myocardial flow reserve, which is an assessment of the absolute blood flow across coronary arteries [50, 60, 63]. A diminished myocardial flow reserve (defined as < 1.9–2.0) is suggestive of underlying vascular dysfunction and microvascular disease [60, 63].

Cardiac MRI

CMR is gaining popularity as a robust non-invasive modality that can accurately assess global and regional systolic left ventricular function, myocardial perfusion, and scar. Owing to its higher spatial resolution, CMR has demonstrated higher diagnostic accuracy compared to SPECT MPI, with a sensitivity of 88.7% and specificity of 83.5% in women [64]. Prognostic value of CMR is similar between men and women [65]. Women with an abnormal dobutamine CMR had a 4-fold higher risk of MI or cardiac death when compared to women with a normal CMR [66]. On the other hand, a normal stress CMR in women is associated with an annual rate of 0.3% of major adverse cardiac events (MACEs) [65].

Advanced stress CMR techniques, including the assessment of myocardial flow reserve and perfusion reserve index, also allow for the detection of impaired coronary vasoreactivity and endothelial dysfunction [67•]. In a study of 113 symptomatic women without obstructive CAD on coronary angiography, 57% were found to have abnormal subendocardial perfusion seen on adenosine stress MRI but not rest images, consistent with coronary microvascular disease [68]. These perfusion defects, even in the absence of obstructive coronary atherosclerosis, were associated with MACE and cardiac death [65]. Females with evidence of ischemia on CMR have an annual MACE rate of 15%, while those without ischemia have an MACE rate of only 0.3% [65].

Coronary computed tomography angiography

CCTA is an emerging anatomic approach to evaluating IHD and provides valuable insights regarding the extent and severity of coronary atherosclerosis, luminal stenosis, plaque composition, and the presence of arterial remodeling [48••, 67•]. CCTA offers excellent risk stratification, segregating women with normal coronary arteries, non-obstructive CAD, and obstructive CAD to cardiac event rates of 0.2, 1.2, and 2.1%, respectively [69]. Importantly, presence of non-obstructive atherosclerosis on CCTA was not benign and associated with a higher symptom burden and 2-fold higher mortality compared to no disease [69].

Coronary angiography

ICA remains the "gold standard" for the diagnosis of obstructive CAD in both men and women. ICA is currently recommended as the initial strategy for CAD evaluation in sudden cardiac death survivors or patients with potentially life-threatening arrhythmias, or those with signs and symptoms of heart failure [49]. Both men and women who have intolerable ischemic symptoms despite appropriate guideline directed medical therapy and who are candidates for revascularization, should undergo ICA [49]. It is also recommended that patients who have a high pretest probability of severe ischemia who are candidates for revascularization should undergo ICA, a recommendation tempered by uncertainty of the added benefit of revascularization above medical therapy in this group of patients [70]. ICA is not without risks, and its incremental value in directing further management should be carefully considered before proceeding.

Nearly two thirds of women with suspected IHD have "normal coronaries" or non-obstructive disease on ICA [37, 42]. Absence of flow-limiting epicardial disease is not necessarily a benign finding as short- and long-term prognoses in these women is poorer compared to the background population without angina [37, 43•, 71]. Performance of advanced angiographic techniques may demonstrate the presence of occult coronary abnormalities, including non-obstructive plaque by intravascular ultrasound, endothelial dysfunction on acetylcholine testing, and microvascular dysfunction on adenosine testing [39, 72]. Despite "normal coronaries" on ICA, there is a high prevalence of atherosclerotic plaque on intravascular ultrasound as coronary artery remodeling may limit the sensitivity of the angiogram for the presence of atherosclerosis [72]. Optical coherence tomography may also provide additional information on plaque morphology [73].

Patients with intermediate (non-obstructive) lesions, and a small subset of patients with visually normal coronaries, may have abnormal fractional flow reserve (FFR), suggesting hemodynamically obstructive disease for which revascularization may be of benefit [49]. Women have been observed to have higher FFR measurements for similar degrees of angiographic stenosis severity when compared to men [74, 75]. Potential explanations for this include smaller myocardial mass supplied by the stenosed vessel, inaccurate visual estimation of stenosis due to smaller vessel size, or a higher prevalence of left ventricular hypertrophy and diastolic dysfunction in women which may impact microvascular function and maximal hyperemia, among others [76]. An FFR-guided strategy of revascularization is similarly beneficial in both sexes [74]. FFR should therefore be employed liberally in evaluation of intermediate lesions in women as symptoms may be due to microvascular dysfunction rather than epicardial CAD.

Prognosis and outcomes in women with IHD

Paradoxically, even though women have a lower burden of atherosclerosis, they experience a higher incidence of angina, worse quality of life, recurrent hospitalization, and mortality [37, 39, 77]. This is in-part explained by the higher prevalence of non-obstructive coronary atherosclerosis and presence of microvascular disease in women [37, 42]. The 5-year event rate for MI, hospitalization for heart failure, stroke, or cardiac death was 16.0% for symptomatic women with mild non-obstructive disease, 7.9% with no atherosclerosis, and 2.4% in asymptomatic women, matched for risk factors [78]. Similarly, symptomatic women with no obstructive coronary disease had a 10-year all-cause mortality rate of 13%, which was 5-fold higher than in an age-matched asymptomatic reference cohort [43•]. Additionally, a large meta-analysis comprising 26 studies reported, patients with endothelial dysfunction and microvascular disease have a 2.3–4.5-fold increased risk of cardiovascular events [79]. Women with non-obstructive coronary artery disease experience worse outcomes than men [80]. Women are three times more likely than men to experience a MACE within the first year of angiography [80]. Furthermore, given recurrent symptoms in absence of flow-limiting stenosis, they have a high rate of repeat coronary angiography (15.7% at 5 years) [81]. Despite these compelling findings, treatment of women with no-flow obstructing lesions often remains limited to reassurance and results in increased hospitalizations, recurrent coronary angiography, and worse outcomes in response to refractory symptoms.

Contemporary challenges and existing knowledge gaps

A large body of evidence suggests that women experience a greater symptom burden and incur more frequent office visits and hospitalizations, resulting in greater healthcare costs [5, 11, 81]. The reasons for the disparity in outcomes are multifactorial and relate to inadequate understanding and appreciation of biological differences, lack of recognition of atypical symptoms and novel risk factors in women, subconscious referral bias, and suboptimal application of existing evidence-based guidelines [11].

Recognition and awareness of IHD in women

Women experience longer delays in seeking medical care, and time from medical contact to revascularization time, exceeding that recommended by guidelines, compared to men [82]. Potential reasons include inadequate awareness of disease burden and the different clinical presentations in women, both by public and the medical community [25••, 83]. In 2014, only 55% women were aware of IHD being the leading cause of death in women, with even lower rates of awareness in ethnic minorities, and women with lower education and income [25••]. Although most women have ≥ 3 risk factors, only 52% considered themselves at risk at the time of their index MI [84]. Even when women recognize they may be having a MI, only 50% seek urgent medical attention [25••, 83]. Women's delay in seeking care may also be related to frequently receiving inaccurate

and inconsistent responses from the medical community, as their symptoms have often being minimized and attributed to non-cardiac etiologies [2]. Concerningly, the rates of awareness are actually worse among physicians with only 39% of primary care physicians viewing IHD as the top concern during routine clinic visits with their female patients [25••]. Furthermore, only 53% cardiologists and 44% primary care physicians utilized the ASCVD risk calculator for risk assessment of their female patients, and women's risk of IHD was consistently underappreciated [25••]. Even when clinicians suspect symptoms of IHD, the diagnostic tools may not be adequately sensitive or specific in women [14, 29].

Summary and recommendations

Although in the last decade there has been an expansion of our understanding of sex-based differences in risks, symptoms, assessment, and intervention of IHD, these biological differences are still underappreciated. The same definition of "typical angina" continues to be used for both sexes, despite this representing a male-pattern of symptomatology. The same conventional risk assessment scores are used in both sexes, excluding the novel risk markers prevalent in women, resulting in underestimation of risk in women [14, 29]. The same normal thresholds for troponin assays are used to determine presence of MI in both sexes, despite data suggesting these thresholds may lack sensitivity in women [85]. Women are often subject to the same diagnostic algorithms as men, which are insufficient to detect the varied ischemic etiologies of chest discomfort in women. Reasons for the suboptimal appreciation of biological differences include underrepresentation of women in clinical trials and registries, and male dominant results being extrapolated to women [86].

Evolving knowledge about microvascular disease needs to be better incorporated into IHD guidelines and practice styles. Presently, there are only a handful of contemporary guidelines to address IHD prevention, diagnosis, and management in women, and these, too, are poorly implemented [11, 25••], highlighting a more pervasive subconscious bias in the medical community. This potentially calls for a system-wide paradigm shift to abandon classic definitions and embrace a more sex-conscious practice of medicine. Adequately powered research to answer gender-focused questions is needed to better establish female-specific risk scores, diagnostic thresholds, diagnostic algorithms, and management pathways. Research comparing the different imaging modalities for diagnosing non-obstructive plaque and microvascular disease may be beneficial. Discovery of novel treatment strategies for women that do not begin with identification of flow-limiting stenosis would be paramount [41]. Improved recognition of the sex-differences must also translate into inclusion of sex- and gender-based curricula into medical training, and at scientific meetings, to transform practice paradigms, along with public health education campaigns to ultimately result in improved IHD outcomes in women.

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Compliance with Ethical Standards

Conflict of Interest

The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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